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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,013	04/04/2006	Rudolf Fahrig	P28506	8056

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GREENBLUM & BERNSTEIN, P.L.C.
1950 ROLAND CLARKE PLACE
RESTON, VA 20191

EXAMINER
HENRY, MICHAEL C

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
09/03/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com
pto@gbpatent.com

Office Action Summary	Application No.	Applicant(s)	
	10/550,013	FAHRIG ET AL.	
	Examiner	Art Unit	
	MICHAEL C. HENRY	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-12,15-22 and 24-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-12, 15-22, 24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 05/27/09 affects the application, 10/550,013 as follows:

1. Claims 8, 15, 18, 19 have been amended. Claims 27 and 28 have been added. The rejections made under 35 U.S.C. 112, second paragraph and under 35 U.S.C. 103(a) in the prior office action mailed 01/28/09 are maintained.
2. The responsive to applicants' arguments is contained herein below.

Claims 8-12, 15-22, 24-28 are pending in application

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-12, 15-22, 24-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 "recites the phrase "a 5-substituted nucleoside comprising (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)". However, the claim is indefinite since it is unclear how a 5-substituted nucleoside can comprise (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) as opposed to being (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU). Also, Claims 27 and 28 recite the phrase "wherein the 5-substituted nucleoside administered during the recovery phase comprises a compound of a given general formula I". However, the claims are indefinite since it is unclear how the 5-substituted nucleoside can comprise a compound of a given general formula I as opposed to being a compound of general formula I. Furthermore, the claims are indefinite since it is unclear how the 5-substituted nucleoside that is administered during the recovery phase can

be both (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) and the given compound of the general formula I

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-12, 15-22, 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fahrig et al. (WO 96/23506, English Translation).

Claim 8 is drawn to a method of increasing apoptotic effect of cytostatics after chemotherapy comprising administering a 5-substituted nucleoside comprising (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), salt, prodrug or mixture thereof, the administering being without administration of a cytostatic, during a recovery phase after a cytostatic chemotherapy cycle. Claim 9 is drawn to said method wherein the administration includes cytostatic and a 5-substituted nucleoside comprising BVDU, a protected form, salt prodrug, or mixture thereof. Claims 10-12, 15-22 and 24-28 are drawn to said method involving the administration of specific amounts of cytostatic and BVDU, specific recovery phase and chemotherapy cycle, and specific concentration of 5-substituted nucleoside in the blood, specific cytostatics and compound of general formula I.

Fahrig et al. disclose that 5'substituted nucleosides in combination with at least one cytostatic can be used in the production of a medicament to prevent or reduce the build-up of

resistance in cytostatic treatment and a medicament containing BVDU and/or its metabolites (see abstract). It should be noted that the apoptotic effect encompasses the cytostatic treatment disclosed by Fahrig et al. Furthermore, Fahrig et al. disclose that BVDU alone appears slightly to lessen the spontaneous degree of gene amplification (see page 10- line 24 to page 11, line 3). In addition, Fahrig et al. disclose that BVDU, in clinically relevant doses, inhibits AMP-induced gene amplification and that the said inhibition is dose dependent (see page 10- line 24 to page 11, line 3). This implies that BVDU has the effect of preventing or reducing the build-up of resistance resulting from cytostatic treatment. In addition, it should be noted that the given compound of general formula I is a known prodrug (Cas # 232925-18-7) of the compound BVDU (see also applicant's specification page 3, last paragraph).

The difference between applicant's claimed method and the method suggested by Fahrig et al. is that Fahrig et al. do not disclose administering said BVDU during the recovery phase after a cytostatic chemotherapy cycle. However, Fahrig et al. suggest that BVDU can cause the apoptotic effect of the cytostatic to be more effective (i.e., increased) due to the build-up of resistance in cytostatic treatment. This implies that BVDU has the effect of preventing or reducing the build-up of resistance resulting from cytostatic treatment. Consequently, a skilled artisan would be motivated to administer BVDU alone to reduce the build-up of resistance resulting from cytostatic treatment and to exclude the administration of more cytostatic which may cause side effects or adverse effects and to optimize or maximize the effectiveness of said cyotostatic especially during a recovery phase after a cytostatic chemotherapy cycle.

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made in view of Fahrig et al., to increase apoptotic effect of cytostatics after

chemotherapy comprising administering said BVDU or a prodrug of BVDU such as the compound of general formula I, during a recovery phase after a cytostatic chemotherapy cycle based on factors such as the severity of the build-up of resistance due to the cytostatic treatment (especially after chemotherapy cycle), the side effects or adverse effects of excess cytostatics build up, the maximum tolerant dose of the cytostatic and the type of individual treated, since Fahrig et al. disclose that BVDU and/or its metabolites can reduce the build-up of resistance in cytostatic treatment.

One having ordinary skill in the art would have been motivated, in view of Fahrig et al. to increase apoptotic effect of cytostatics after chemotherapy comprising administering said BVDU or a prodrug of BVDU such as the compound of general formula I, during a recovery phase after a cytostatic chemotherapy cycle based on factors such as the severity of the build-up of resistance in cytostatic treatment (especially after chemotherapy cycle), the side effects or adverse effects of excess cytostatics, the tolerant dose of the cytostatic and the type of individual treated, since Fahrig et al. disclose that BVDU and/or its metabolites can reduce the build-up of resistance in cytostatic treatment. It should be noted that the use of prodrugs is common in the art and is well within the purview of a skilled artisan. Also, It should be note that the use of specific ratios of drugs, agents or cytostatics and frequency of administration depends on factors such as the type and severity of the condition treated and the kind of subject treated.

Response to Arguments

Applicant's arguments with respect to claims 8-12, 15-22, 24-28 have been considered but are not found convincing.

The applicant argues that the Fahrig PCT teaches away from the presently-claimed invention because the Fahrig PCT suggests a theory of action that suggests that administering a 5'-substitute nucleoside during a recovery phase would be ineffective. In particular, the Fahrig PCT teaches that 5'-substituted nucleosides work during administration of a cytostatic by inhibiting the mechanism by which cancer cells shuttle the cytostatic out of the cell. By inhibiting this mechanism, it is suggested that the 5'-substituted nucleoside increases concentration of the cytotoxic agent, thereby leading to increased cell death (apoptosis). This teaches the person of skill in the art that administering a 5'-substituted nucleoside during a recovery phase (when there is no cytostatic present) would be ineffective, because doing so would only inhibit a mechanism that, because of the absence of cytostatic, is already non-operational.

However, Fahrig does not teach away. On the contrary, based on the teaching of WO 96/23506 those of skill in the art would expect the administration of 5'substituted nucleoside during a recovery phase would be effective in that it would further facilitate the incorporation of cytostatics into the cells depending factors such as on the amount of cytostatic that is built up during the recovery phase after a cytostatic chemotherapy cycle and the rate at which said cytostatic is incorporated into the cells. Furthermore, the reduction in gene amplification means enhanced take-up of cytostatics (or reduction in the build-up of resistance) and consequently an increase or enhanced apoptosis effect or cytostatic treatment. In addition, the reduction in the shuttling of the cytostatic agent out of the cell due to the reduction or inhibition of spontaneous degree of gene amplification promotes, increases or enhances the apoptosis or cytostatic treatment. Also, it should be noted that the recovery phase is not limited to or defined by a

specific time period relative to or after said cytostatic administration and there is no specific amount of cytostatic agent that is being used in Applicant's claimed treatment and consequently cytostatic agent would be present during the recovery phase.

The Applicant argues because of the effect that 5'-substituted nucleosides have on inhibiting shuttling cytotoxic agents out of cancer cells, one of ordinary skill in the art would have expected such compounds not to have any significant effect if administered during a recovery phase after a cytostatic chemotherapy cycle. On the contrary however, based on the teaching of WO 96/23506 those of skill in the art would expect the administration of 5'substituted nucleoside during a recovery phase would be effective in that it would further facilitate the incorporation of cytostatics into the cells depending factors such as on the amount of cytostatic that is built up during the recovery phase after a cytostatic chemotherapy cycle and the rate at which said cytostatic is incorporated into the cells. Furthermore, the reduction in gene amplification means enhanced take-up of cytostatics (or reduction in the build-up of resistance) and consequently an increase or enhanced apoptosis effect or cytostatic treatment. In addition, the reduction in the shuttling of the cytostatic agent out of the cell due to the reduction or inhibition of spontaneous degree of gene amplification promotes, increases or enhances the apoptosis or cytostatic treatment. Also, it should be noted that the recovery phase is not limited to or defined by a specific time period relative to or after said cytostatic administration and there is no specific amount of cytostatic agent that is being used in Applicant's claimed treatment and consequently cytostatic agent would be present during the recovery phase.

The applicant argues that the present application presents the surprising discovery that administration of a 5' substituted nucleoside during a recovery phase unexpectedly provides

better chemotherapeutic results than where there is no such administration during the recovery phase. However, one of ordinary skill would expect that the administration of a 5' substituted nucleoside during a recovery phase would provide better chemotherapeutic results than where there is no such administration during the recovery phase based and since Fahrig et al. disclose that BVDU and/or its metabolites can reduce the build-up of resistance in cytostatic treatment on the teaching Fahrig et al. (see above rejections). It should be noted that the unexpected results presented by applicant was not obtained for the instant invention. Furthermore, it is important to note that if applicant intends to rely on unexpected or unforeseen results, attention is invited to M.P.E.P. § 716. Absent clear, convincing, side-by-side date demonstrating unobviousness vis-á-vis the prior art commensurate with the scope of protection sought, the claims are considered prima facie obvious. Also, Attorney's arguments of unexpected results cannot take the place of evidence in the record. In re DeBlauwe, 736 F.2d 699, 705, 222 U.S.P.Q. 191, 196 (Fed. Cir. 1984).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652. The examiner can normally be reached on 8.30am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael C. Henry
August 30, 2009.

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623